Principles of Cardiac Electric Propagation and Their Implications for Re-entrant Arrhythmias

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The study of clinical electrophysiology essentially comprises examining how electric excitation develops and spreads through the millions of cells that constitute the heart. Given the enormous number of cells in a human heart, there is an extremely large number of possible ways that the heart can behave. We encounter rhythms across the spectrum from the organized and orderly behavior of sinus rhythm through repetitive continuous excitation (via reentry) in structurally defined circuits like atrial flutter and, finally, the complex, dynamic, and disorganized behavior of fibrillation. Despite these myriad possibilities, one can apply a basic understanding of the principles of propagation to predict how cardiac tissue will behave under varied circumstances and in response to various manipulations.

In this article, we review the principles of propagation and how these can be used to understand reentry of all degrees of complexity. We use these principles to explain the mechanisms by which antiarrhythmic medications and ablation can terminate and prevent reentry. This article is not intended to be an exhaustive description of the physiology of cardiac propagation, rather, it is meant to capture the essence of propagation with sufficient detail to provide an intuitive feel for the interplay of the physiological features relevant to propagation.

The figures and videos used in this article were created using a computational model of cardiac propagation (VisibleEP LLC, Colchester, VT). It is a hybrid between a physics-based and cellular automaton model. The model incorporates the fundamental features of propagation without modeling individual ion channels. The model manifests several relevant emergent properties, for example, electrotonic interactions, restitution of action potential duration, and conduction velocity as well as source–sink balance–dependent propagation.

Impulse Propagation

Cell Excitation

A cell becomes excited when the balance of inward and outward currents passes a critical point after which inward currents exceed outward and an action potential ensues. When the membrane voltage of a cell rises above the activation threshold of its depolarizing currents (sodium current \(I_{Na}^{-}\)), its inward current grows. Meanwhile, as membrane voltage increases, the amplitude of outward currents decreases. Excitation (or the lack thereof) is dependent on a delicate balance between these currents.

To reach threshold, the net transmembrane current must be sufficient to discharge the membrane capacitance. This term is not necessarily intuitive for those unfamiliar with physics or engineering but the concept is in fact fairly simple. The membrane separates charges across the space between its inner and outer surfaces, resulting in a voltage gradient. The size of the voltage gradient is determined by the number of charges separated and the distance by which they are separated. Think of the force that is required to keep these charges from wandering away from the cell surface. This force is generated by the electric attraction to opposite charges on the other side of the membrane. The thinner the membrane, the closer together the charges are to each other and the larger force they can exert to resist wandering off (ie, the distance across the faces of a capacitor is inversely proportional to its capacity to hold charges on its surface—its capacitance). Therefore, the capacitance is determined by the surface area of the membrane and its thickness (how far apart it separates charges). As capacitance increases, the voltage change that results from addition of a single charge to the membrane is reduced. Therefore, an increase in capacitance means more charge is required per millivolt increase in membrane voltage. Because membrane thickness is the same in all cardiac cells, capacitance varies directly with cell size (attributable to a larger surface area) and inversely with intercellular resistance (well-connected groups of cells act much like 1 large cell). Consequently, larger cells or well-connected groups of cells are harder to excite than smaller poorly connected cells (more current is required to reach activation threshold).

Cardiac membranes can simultaneously accommodate inward and outward currents (via separate ion channels/exchangers/pumps). Membrane depolarization is determined not by inward current alone but rather by net inward current. Therefore, if there are both inward and outward currents, then the amount of depolarization (or repolarization) is determined by the balance of these currents. In their resting state, the majority of open channels in typical atrial and ventricular cells are potassium (K+) channels (in fact this is why the resting...
membrane potential is nearly equal to the reversal potential for K⁺). In the absence of other open ion channels, K⁺ flows into or out of the cell until the forces of the electric gradient (the membrane voltage) is equal to and opposite from the force of the chemical gradient. Any further current flow would reverse the balance of forces and, therefore, reverse the current direction until equilibrium is restored; hence, the name reversal potential. As current enters a cell (eg, via gap junctions from a neighbor), the membrane will begin to depolarize. This depolarization reduces the force preventing K⁺ from traveling down its concentration gradient out of the cell. Once this concentration gradient force exceeds the voltage gradient counterforce, K⁺ flows out of the cell. This, in turn, results in membrane repolarization. Therefore, for inward current to result in depolarization, its magnitude must be greater than the outward current that it unleashes. The effect of outward K⁺ current to resist membrane depolarization (keeping voltage fixed) is sometimes referred to as a voltage clamping effect. 3 The potassium channel open at rest is called the inward rectifier (its current is Iᵢᵣ). Cells that have a large number of inward rectifier channels have a resting membrane potential close to the K⁺ reversal potential and resist depolarization; via the voltage clamping action of Iᵢᵣ, such cells require more depolarizing current to become excited. Depolarization has the dual effect of (1) activating inward currents (if their threshold is reached) and (2) decreasing outward currents if depolarization is sufficient to cause inactivation of Iᵢᵣ.

**Source–Sink Relationship**

Propagation refers not simply to cell excitation but specifically to excitation that results from depolarizing current spreading from a cell to its neighbors. 4 It is useful to talk about electric propagation in terms of the source of depolarizing current and the sink of tissue that is to be depolarized. The source can be conceived of as a bucket filled with electric charge and the sink as a separate bucket into which the source charge is poured (Figure 1A; Video I in the online-only Data Supplement). When the water level in the sink-bucket reaches the threshold for activation (via gap-junction-flow from electrically connected source cells), the bucket is excited (filling completely with charge from its own ion channels). This sink-bucket then becomes part of the source. With this analogy, one can think of the amount of charge poured into the sink, in excess of that required to reach threshold, as the safety factor (Figure 1B). To be precise, the safety factor is a measure of the ratio between the amount of charge supplied (the source) and the amount of charge required for excitation (the sink); thus, with source–sink balance, there is a ratio of 1, any less and propagation would fail. The bucket analogy helps to visualize the parameters that affect the size of the sink. One can envision the increased capacitance of multiple cells connected in a syncytium, as ≥2 buckets connected at their bases by tubes (Figure 1C). The resistance of that tube (gap junctions) will influence the distribution of charge poured into the first sink-bucket. 5 With high intercellular resistance, the majority of the charge poured into the first bucket will contribute to raising the voltage level of that bucket (with only a small trickle of charge flowing into the second bucket). As the intercellular resistance is reduced, the rate of rise of voltage in the first and second buckets progressively equalizes. With sufficiently low resistance, the sink has effectively doubled in size (and the amount of depolarization of each membrane has been reduced by half). Therefore, as the intercellular resistance goes down (and number of connected cells is increased), the size of the sink is increased. With the source amplitude held constant while the sink size is increased, the source–sink ratio is reduced. As the source–sink ratio diminishes, conduction velocity decreases; it takes longer for each cell to reach the threshold that reduces the rate of propagation. Propagation requires 2 steps: (1) each cell must reach activation threshold and initiate an action potential, and (2) this cell then provides current to its neighbor. If the first step takes a longer time (eg, by virtue of a slower rise to threshold secondary to increased sink), then propagation to the next cell will take longer, that is, decreased conduction velocity. With a sufficient decrease in the source–sink ratio, safety factor diminishes to <1, excitation fails, and propagation ceases (source–sink mismatch).

In the bucket analogy, the net depolarizing current is the inward (or in this case upward) current. Leak current (or outward/downward current) is analogous to a leak in the bottom of the bucket, the size of which determines the net current (Figure 1D). One can appreciate the elegance and nuance in the relevant physiology when one considers that (1) outward current leads to repolarization that in turn (2) leads to greater recovery from inactivation of the inward current channels and hence (3) an increase in the availability of excitatory current in response to subsequent depolarization. The parameters that influence source sink balance are illustrated in Figure 2.

**Tissue Architecture and the Source–Sink Relationship**

All else being equal, the source–sink balance is determined by the number of source cells and the number of sink cells to which they are connected. The physical arrangement of cells in
a tissue will influence this balance. An example of structurally determined source–sink mismatch occurs when a relatively thin bundle of fibers expands to a broader region of tissue. At this junction, the fiber end provides a smaller source than the sink of the broader band of tissue to which it is connected. With sufficient mismatch, this can result in conduction failure. Interestingly, in this case, the source–sink balance is asymmetrical. When propagation proceeds in the opposite direction (from broad band into narrow bundle), the source is larger than the sink and conduction succeeds. This tissue configuration can, thus, result in unidirectional conduction block and is a potential mechanism for concealed accessory pathways.6,7

Wave Curvature and the Source–Sink Relationship
If you consider, the physical dimensions of a curved wavefront the source and sink are not equal (Figure 3A and 3B). In a convex wavefront, the source is smaller than the sink; therefore, convex wavefronts conduct more slowly than flat or concave wavefronts.8,9 Thus, the rate and reliability of excitation is proportional to wave curvature; as curvature increases conduction velocity decreases until critical curvature results in propagation failure. This is the basis for one of the most complex rhythm disturbances, fibrillation. Spiral waves have a curved leading edge, in which the curvature is progressively greater toward the spiral center. As curvature increases, conduction velocity decreases. At the spiral center, the curvature is large enough that propagation fails (because of source–sink mismatch) creating a core of unexcited tissue around which rotation occurs.10,11

Re-entry
Although there are several mechanisms for abnormal heart rhythms, by far the most common clinical arrhythmias are attributable to re-entry. The fundamental characteristic of re-entry is that ongoing electric activity results from continuous propagation (as opposed to repeated de novo focal impulse formation).

The general concept of re-entry is straightforward: waves of activation propagate in a closed loop returning to reexcite the cells within the re-entry circuit. Because of the refractory properties of the heart, a wave of excitation cannot simply reverse directions; re-entry requires separate paths for conduction away from and back toward each site in the circuit.4,12,13

The details of circuit formation can be quite varied and in some cases quite complex. In the simplest case, the circuit is structurally defined; physically separated conduction paths link to form a closed loop (eg, atrial flutter). Circuits can also be composed of paths that are separated because of functional cell–cell dissociation (eg, rotors). In all cases, re-entry requires (1) a closed loop of excitable tissue (2) conduction block around the circuit in 1 direction with successful conduction in the other direction, and (3) a conduction time around the circuit that is longer than the refractory period of any component of the circuit.

We have previously described re-entry circuits from a topological perspective.14 Consider a finite 2-dimensional sheet of excitable cells. The edges of the sheet form a boundary; topologically this is a bounded plane. A wave of excitation will traverse the sheet and extinguish at its edges (Figure 4A).
If there is a region in which cells are disconnected within the sheet, then a closed loop exists, which has the potential to support re-entry (Figure 4B) provided conditions 2 and 3 are met. Topologically, this region of disconnection is an inner boundary. Technically, if there is >1 boundary, then there is no reason to label 1 inner and 1 outer; all that matters for circuit creation is that there are 2 boundaries that are not connected to each other. It is irrelevant whether the disconnection is because of physical factors (eg, scar/no gap junctions or a physical hole) or functional factors (source–sink mismatch or refractory conduction block); in either case, the result is an interrupted bounded plane. The value of considering re-entry circuits from a topological perspective is the generalizability with which it applies to the full range of possible circuits. Despite their potential myriad constituents, all re-entrant circuits must be interrupted bounded planes. The other parsimonious result of a topological perspective is the unification it confers on all treatments for re-entry: circuit transection by any means results in termination (topologically, regardless of the means, all circuit transections constitute transformation back to an uninterrupted bounded plane). In topology, 2 surfaces are considered homomorphic (the same) if by stretching, but not cutting, or pasting the surfaces can be transformed one to the other. Thus, all re-entry circuits are homomorphic, and all transected circuits are homomorphic.

A circuit can be transected physically as with ablation or functionally as with antiarrhythmic medications. In the latter case, either reduction of excitability or extension of refractory period results in complete circuit transection with a continuous line of unexcited cells spanning from the tissue edge to the inner boundary. In each case, an interrupted plane has been transformed into an uninterrupted plane (Figure 5).

**Complex Re-entrant Circuits: Rotors and Multiwavelet Re-entry**

Spiral waves and multiwavelet re-entry are 2 interesting and important manifestations of the principles of propagation. As described, wave curvature influences source–sink balance. Spiral waves have a curved leading edge, in which curvature is progressively greater toward the spiral center (Figure 3C). As curvature increases (toward the center of rotation), conduction velocity decreases. At the spiral center, the curvature is large enough that wave curvature reduces safety factor to <1 and propagation fails (because of source–sink mismatch) creating a core of unexcited tissue around which rotation occurs.10,11 If the wave length at the innermost aspect of the spiral wave is less than the path length around the unexcited sink, then the core will be circular (or will be a point). If the wavelength is longer than the path length, then the wave will continue laterally along its own refractory tail until it encounters excitable tissue at which point it can turn. This produces an elongated core. If the conduction velocity around the core is uniform, then the rotor will remain fixed in space. Alternatively, if conduction velocity is greater in one part of rotation than another, then the core will drift.15 Activation waves propagate radially from the rotor core producing a spiral wave (radial propagation, with progressive phase shift, appears as rotation). If the edge of this spiral wave encounters unexcitable tissue, then it will break. If the newly created wave-ends begin rotation, then the so-called daughter-waves are formed.15–18 In the most complex iterations, re-entry can comprise multiple meandering and dividing waves at times with spiral wave life span lasting for less than a single rotation. Thus, activation during multiwavelet re-entry can be quite complex as conduction paths change and re-entry circuits are formed or annihilated. The cardinal features of re-entry, refractoriness, and conduction velocity vary across the heart and over time. Both refractoriness and conduction velocity are rate dependent (ie, possess restitution), which markedly increases the complex, nonlinear nature of fibrillation.19–21

**Terminating and Preventing Re-entrant Rhythms**

The mechanism of re-entry provides insight into the strategies that will result in its termination: if re-entry requires closed circuits, then prevention/termination requires...
transection of these circuits. Transection can be achieved in several different ways. In the case of fixed anatomic circuits, one can simply physically transect the circuit (eg, linear ablation across the cavotricuspid isthmus for atrial flutter). Another approach is to prolong the wavelength (by increasing refractory period) sufficiently that wavelength exceeds path length, head meets tail, and the circuit is transected by a line of functional block.

It is important to note that wavelength (conduction velocity×refractory period) can be increased by prolonging action potential duration or increasing conduction velocity. All else being equal, if one increases refractory period insufficiently to result in wavelength greater than path length, then tachycardia persists but without ill effect. If on the other hand, one increases conduction velocity, but not sufficiently to make wavelength greater than path length, then tachycardia accelerates. Therefore, increasing refractory period is a safer anti-arrhythmic strategy than increasing conduction velocity. All else is not equal: increasing refractory period (by prolonging action potential duration) has the potential to produce triggered firing, torsade de pointes, and sudden death.

Antiarrhythmic Medication for Re-entrant Rhythms
The antiarrhythmic approach to treating multiwavelet re-entry in atrial fibrillation (AF) can include decreasing excitation (thereby increasing the minimum sustainable curvature, increasing core size, meander, and core collision–probability) or increasing action potential duration and thereby wavelength (again increasing the probability of core collision/annihilation).\(^2\) Unfortunately, as AF progresses electric remodeling of the atria render it is progressively more conducive to perpetuation of re-entry, such that the antiarrhythmic dose required to achieve sufficient action potential duration prolongation in the atria can result in proarrhythmia in the ventricles.

Ablation for Re-entrant Rhythms
It is relatively straightforward to see how ablation can be used to transect a spatially fixed circuit but less clear how delivery of stationary ablation lesions can reliably transect moving functional circuits. Circuits are spontaneously transected when their core collides with the tissue edge (annulus) or with a line of conduction block that is contiguous with the tissue edge (Figure 6; Video II in the online-only Data Supplement). Based on this premise, it is not surprising that the probability that multiwavelet re-entry will perpetuate is inversely proportional to the probability of such collisions.\(^1\) As tissue area is increased (while keeping tissue boundary fixed) the probability of core/boundary collision is reduced and perpetuation probability enhanced. If the area over which waves meander is reduced or the number of waves is increased, then the probability that all waves will collide/annihilate is reduced. Thus, atrial remodeling promotes fibrillation by decreasing the length-to-area ratio (chamber dilation [area] is greater than annular dilation [boundary length]) and by decreasing wavelength (conduction velocity is decreased and action potential duration is decreased). Decreased wavelength allows more

Figure 6. Rotor termination results from circuit transection via core collision with tissue boundary. The rotor core (black dot) moves closer to the tissue edge (arrows) with each rotation (1–4). On collision of the core with the tissue edge (5) the circuit is transected, and reentry is terminated (6). Color bar indicates % depolarization; and gray, subthreshold voltage.

Figure 7. Rotor ablation requires a linear lesion from the rotor core to the tissue edge. A, Focal ablation at a rotor core converts a functional circuit (spiral wave) into a structural circuit but does not eliminate reentry. B, If a linear lesion does not extend to the rotor core, then reentry continues (similar to a cavotricuspid isthmus ablation line that fails to extend all the way to the Eustachian ridge). C, An ablation line from the rotor core to the tissue edge transects the reentry circuit. Instead of circulating around its core, the wave end travels along the ablation line and ultimately terminates at the tissue edge. Color bar indicates % depolarization; and gray, subthreshold voltage.
waves to fit inside a smaller area. The circuit transection/ collision-probability perspective on AF perpetuation suggests the means to reduce atrial fibrillogenicity (tendency to maintain fibrillation). One can increase the length-to-area ratio by adding linear ablation lesions. To transect a rotor circuit, an ablation line must extend from the tissue edge to the rotor core (Figure 7). Focal ablation at the center of a rotor simply converts the functional block at its core into structural block; focal ablation transforms spiral wave re-entry into fixed anatomic re-entry (Video III in the online-only Data Supplement). Interestingly, although focal ablation at a rotor core does not produce circuit transection and direct termination, it has been shown that focal ablation can increase the range over which a rotor core meanders.23 This can ultimately produce rotor collision with a tissue boundary and, therefore, circuit interruption; thus, focal ablation can indirectly result in rotor annihilation.

Mass Hypothesis of Atrial Fibrillation

It was observed as early as the beginning of the twentieth century that the propensity of a tissue to maintain fibrillation is proportional to its area.24,25 Furthermore, it was recognized that total surface area was not the only determinant of fibrillogenicity; fibrillation terminates more quickly in long, skinny strips of tissue compared with square tissue of the same total area. It was this latter finding that led Garrey to postulate that fibrillation is a re-entrant rhythm requiring a minimum radius within which to turn around. This notion was subsequently capitalized on by Cox when he developed the Maze procedure.26,27 He hypothesized that if the atria are divided into segments too small to allow a re-entrant circuit, then AF cannot be maintained.

In computer modeling studies, we have made the following observations: multiwavelet re-entry terminates when rotor cores collide with a tissue outer boundary and that collision is more likely as the ratio of tissue boundary to tissue area is increased (ie, through addition of linear ablation contiguous with the tissue edge). It was further shown that when the distribution of rotor cores is concentrated in certain regions (based on tissue physiology and architecture), the probability of collision is greatest when ablation lines are placed in the regions with higher rotor density.

Conclusion

Understanding of propagation through excitable tissue is fundamental to the study of cardiac electrophysiology and the management of arrhythmias. Propagation is about cells exciting their neighbors. Its success or failure is determined by the adequacy with which current flow from excited cells raises the voltage of their unexcited neighbors to the threshold for activation. A critical feature of this interaction is the relative sizes of the current source and sink. Many of the determinants of conduction result from the dynamically evolving context of local tissue environments. This emergent quality of propagation makes electrophysiology deep and rich. Given the heterogeneity of its physiological properties and the complexity of its structural geometry, cardiac tissue is capable of a staggeringly large number of possible excitation patterns. A firm grasp of the principles of propagation allows one to better understand and manipulate cardiac electrophysiology.

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References


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SUPPLEMENTAL MATERIAL

Video 1: Source Sink Relationship. If source charge is sufficient to raise neighboring sink cells to their threshold for activation propagation succeeds. Any excess charge (beyond that required to reach threshold) contributes to the safety factor. Intercellular connections increase sink size; as resistance decreases sink size increases. Conduction velocity progressively decreases (as sink increases) until the source is insufficient to raise sink cells to threshold and propagation fails. Outward current in sink cells increases sink size. As the gradient between membrane voltage and activation threshold increases sink size increases.

Video 2: Rotor Termination. When a rotor’s core hits the tissue boundary its circuit is interrupted and reentry terminates.

Video 3: Ablation of Rotors Requires Linear Lesions. Ablation at the center of a rotors transforms a functional circuit into a structural circuit but does not terminate reentry; path length is increased so tachycardia cycle length is decreased. Termination requires complete circuit transection.